

## **Supplementary Material**

**Supplemental Table 1:** Results from ANCOVA analysis comparing AKI cause and kidney function

**Supplemental Table 2:** Comparison of patient characteristics in those with vs without CRP and uRBP/Cr labs

**Supplemental Table 3:** Histologic features of biopsied patients in the ICI-AKI and non-ICI-AKI and biomarker levels, adjusting for medication usage at ICI initiation and within 14 days prior to AKI

**Supplemental Table 4:** Kidney function and biomarker levels over time, overall and by cause of AKI

**Supplemental Table 5:** Comparison of Characteristics among n=16 patients with ICI-AKI who were rechallenged, overall and by AKI status after rechallenge,

**Supplemental Figure 1:** Boxplot overlaid with jitterplot of log (CRP\*uRBP/cr), by cause of AKI. The boxes extend from the 25th to the 75th percentile and are bisected by the median; the whiskers extend to the most extreme value within 1.5 of the the interquartile range. CRP, C-reactive protein; uRBP/Cr, urine retinol binding protein-to-creatinine ratio.

**Supplemental Figure 2a:** Longitudinal patient trajectory data of kidney function over follow-up, by AKI cause

**Supplemental Figure 2b:** Longitudinal patient trajectory data of biomarker labs over follow-up, by AKI cause

**Supplemental Figure 3:** Kaplan Meier curve of survival time in months among those rechallenged vs not rechallenged.

**Supplemental Figure 4:** Flow chart of rechallenge and recurrence of ICI-AKI. ICI, immune checkpoint inhibitor; AIN, acute interstitial nephritis; RRT, renal replacement therapy.

STROBE statement (PDF) Supplementary information is available at KI Report's website

**Table S1.** Results from ANCOVA analysis comparing AKI cause and kidney function and biomarker levels, adjusting for medication usage at ICI initiation and within 14 days prior to AKI

Model Parameters	Cause of AKI (ICI-AKI vs non-ICI-AKI)	
	Estimate (SE)	P
<b>Adjusted for medication at time of ICI</b>		
Ln(uRBP/Cr (mcg/g Cr))	2.77 (0.93)	<b>0.003</b>
Ln(CRP (mg/L))	2.56 (0.38)	<b>&lt;0.001</b>
Ln(SCr (mg/dL))	0.38 (0.14)	<b>0.007</b>
Ln(eGFR (mL/min/1.73m <sup>2</sup> ))	-0.41 (0.14)	<b>0.013</b>
<b>Adjusted for medication within 14 days prior to AKI</b>		
Ln(uRBP/Cr (mcg/g Cr))	2.77 (0.85)	<b>0.001</b>
Ln(CRP (mg/L))	2.43 (0.39)	<b>&lt;0.001</b>
Ln(SCr (mg/dL))	0.35 (0.14)	<b>0.012</b>
Ln(eGFR (mL/min/1.73m <sup>2</sup> ))	-0.36 (0.16)	<b>0.023</b>

Kidney function and biomarker levels were modeled using the natural log transformation due to their skewed distributions.

**Table S2.** Comparison of patient characteristics in those with vs without CRP and uRBP/Cr labs

Patient Characteristics	Present CRP and uRBP/Cr labs (N=16)	Missing CRP and/or uRBP/Cr labs (N=34)	p value
<b>At time of ICI initiation</b>			
Age at time of AKI (years), mean (SD)	66.4 (6.6)	67.3 (11.3)	0.78
Gender,n(%)			0.23
Male	6 (37.5%)	19 (55.9%)	
Female	10 (62.5%)	15 (44.1%)	
eGFR, median [IQR] mL/min/1.73m <sup>2</sup>	77.7 [64.0, 83.8]	77.9 [58.3, 86.8]	0.88
HTN, %y	11 (68.8%)	21 (61.8%)	0.76
DM, %y	0 (0.0%)	6 (17.6%)	0.16
CKD, %y	2 (12.5%)	7 (20.6%)	0.70
COPD, %y	0 (0.0%)	7 (20.6%)	0.081
ICI type <sup>a, b, c, d, e</sup> , n (%)			0.17
CTLA-4	0 (0.0%)	1 (2.9%)	
PD-1	14 (87.5%)	19 (55.9%)	
PD-L1	1 (6.3%)	9 (26.5%)	
Combo	1 (6.3%)	5 (14.7%)	
History of autoimmune disease, %y	1 (6.3%)	2 (5.9%)	0.96
Asthma, %y	1 (6.3%)	1 (2.9%)	0.54
Psoriasis, %y	0 (0.0%)	1 (2.9%)	>0.99
Malignancy treated with ICPI, n(%)			0.54
Melanoma	3 (18.8%)	11 (32.4%)	
Lung adenocarcinoma	6 (37.5%)	9 (26.5%)	
Lung small cell	2 (12.5%)	4 (11.8%)	
Head and neck cancer	1 (6.3%)	1 (2.9%)	
Renal Cell	3 (18.8%)	3 (8.8%)	
Bladder/Urothelial	1 (6.3%)	1 (2.9%)	
Other	0 (0.0%)	5 (14.7%)	
PD-L1 tumor marker, n(%)	-	-	0.43
Not done	10 (62.5%)	25 (73.5%)	
done	6 (37.5%)	9 (26.5%)	
Percent PD-L1 among tests done, median [IQR]	75.0 [0.0, 90.0]	20.0 [5.0, 60.0]	0.55
TNI drug, %y	6 (37.5%)	18 (52.9%)	0.31
Type of Medication	-	-	-
PPI	6 (37.5%)	17 (50.0%)	0.55
Antibiotics	0 (0.0%)	0 (0.0%)	-
NSAIDS	0 (0.0%)	2 (5.9%)	>0.99
Other	0 (0.0%)	1 (2.9%)	>0.99
<b>Within 1 month prior to AKI</b>			
Cisplatin, %y	1 (6.3%)	2 (5.9%)	>0.99
TKI/VEGF, %y	2 (12.5%)	3 (8.8%)	0.65
<b>&gt;14 days prior to AKI†</b>			
Any IRAE (1+)	7 (43.8%)	12 (35.3%)	0.57
Subtype			
Rash, %y	1 (6.3%)	5 (14.7%)	0.65
Colitis, %y	1 (6.3%)	2 (5.9%)	>0.99
Hepatitis, %y	2 (12.5%)	2 (5.9%)	0.58
Thyroid Disease, %y	2 (12.5%)	6 (17.6%)	>0.99
Hypophysitis, %y	0 (0.0%)	1 (2.9%)	>0.99
Type 1 DM, %y	1 (6.3%)	0 (0.0%)	0.32
Other, %y	4 (25.0%)	3 (8.8%)	0.19

Within 14 days prior to AKI†			
Patient Characteristics	Present	Missing	p value
	CRP and uRBP/Cr labs (N=16)	CRP and/or uRBP/Cr labs (N=34)	
<b>TNI drug, %y</b>	11 (68.8%)	23 (67.6%)	0.94
<b>Type of Medication, %y</b>	-	-	-
Antibiotics	5 (31.3%)	1 (2.9%)	<b>0.010</b>
NSAIDS	3 (18.8%)	7 (20.6%)	>0.99
PPI	7 (43.8%)	21 (61.8%)	0.36
<b>Any IRAE (1+)</b>	3 (18.8%)	10 (29.4%)	0.42
<b>Subtype</b>			
Rash, %y	0 (0.0%)	2 (5.9%)	>0.99
Colitis, %y	1 (6.3%)	2 (5.9%)	>0.99
Hepatitis, %y	0 (0.0%)	2 (5.9%)	>0.99
Pneumonitis, %y	0 (0.0%)	5 (14.7%)	0.16
Myocarditis, %y	0 (0.0%)	1 (2.9%)	>0.99
Other, %y	2 (12.5%)	2 (5.9%)	0.58
<b>Time of AKI</b>			
<b>AKI Stage*, %n</b>	-	-	<b>0.014</b>
Stage 1	11 (68.8%)	9 (26.5%)	
Stage 2	2 (12.5%)	15 (44.1%)	
Stage 3	3 (18.8%)	10 (29.4%)	
<b>After AKI</b>			
<b>Complete renal recovery within 3 months, %y</b>	7 (43.8%)	16 (47.1%)	0.83

Race was not considered in the table since the cohort was all Caucasian.

COPD, chronic obstructive pulmonary disease; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; Combo, combination.

No pts had CHF or chronic liver disease.

Unless otherwise indicated, timing is at initiation of ICI therapy.

a Denotes all ICPis ever received.

b Ipilimumab was the ICI in 100% of those who received an anti-CTLA-4 antibody.

c Nivolumab or pembrolizumab or cemiplimab were the anti-PD-1 antibodies.

d Atezolizumab, avelumab, durvalumab were the anti-PD-L1 antibodies.

e Ipilimumab/nivolumab was the combination therapy regimen

NE=Not estimable

†There were no cases of Pneumonitis, Primary Adrenal Insufficiency, or Myocarditis >14 days prior to AKI.

‡There were no cases of Thyroid disease, Hypophysitis, Primary Adrenal Insufficiency, or Type 1 DM within 14 days prior to AKI.

**Table S3:** Histologic features of biopsied patients in the ICI-AKI and non-ICI-AKI group

Histologic Features, n (%)	Non-ICI-AKI (n=4)	ICI-AKI (n=14)
<b>Acute interstitial nephritis</b>	0 (0%)	14 (100%)
<b>Acute tubular injury</b>	2 (50%)	12 (86%)
<b>Granulomatous features</b>	0 (0%)	0 (0%)
<b>Tissue eosinophilia</b>	0 (0%)	6 (43%)
<b>Tubulitis, moderate to severe</b>	0 (0%)	7 (50%)
<b>Glomerular pathology*</b>	3 (75%)	1 (7%)
<b>Interstitial fibrosis/tubular atrophy</b>		
None/mild	3 (75%)	11 (79%)
Moderate	1 (25%)	3 (21%)
<b>Glomerulosclerosis</b>		
None/mild	4 (100%)	14 (100%)
Endothelialitis	0 (0%)	1 (7%)
<b>Immunofluorescence microcopy</b>		
<b>Glomerular deposits</b>		
Minimal mesangial IgM	1 (25%)	4 (29%)
TBM deposits (IF & EM)	0 (0%)	0 (0%)

Abbreviations: TBM, Tubular basement membranes; IF, Immunofluorescence;  
EM: electron microscopy

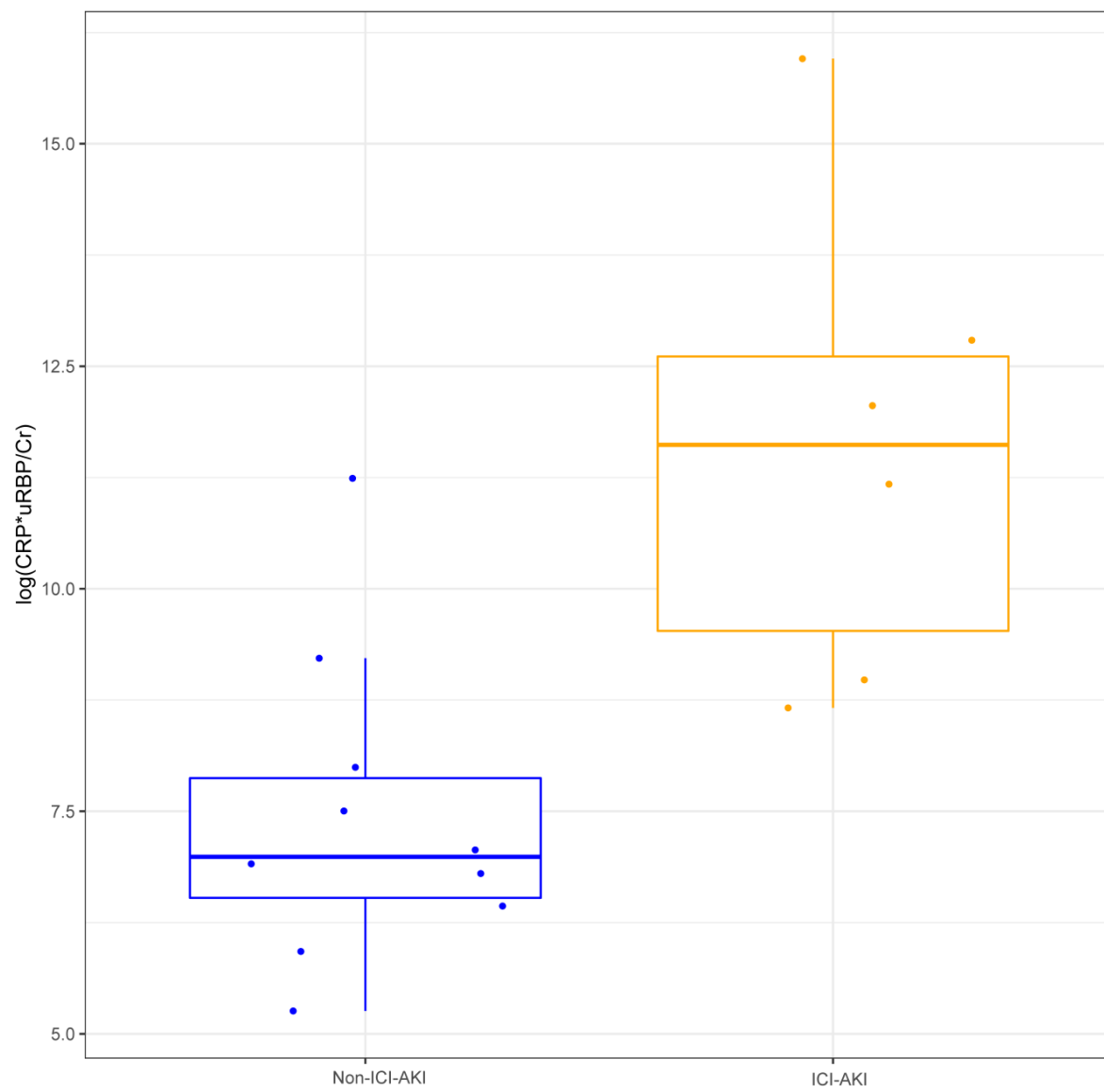
\*Mesangial sclerosis and glomerulomegaly

**Table S4:** Kidney function and biomarker levels over time, overall and by cause of AKI

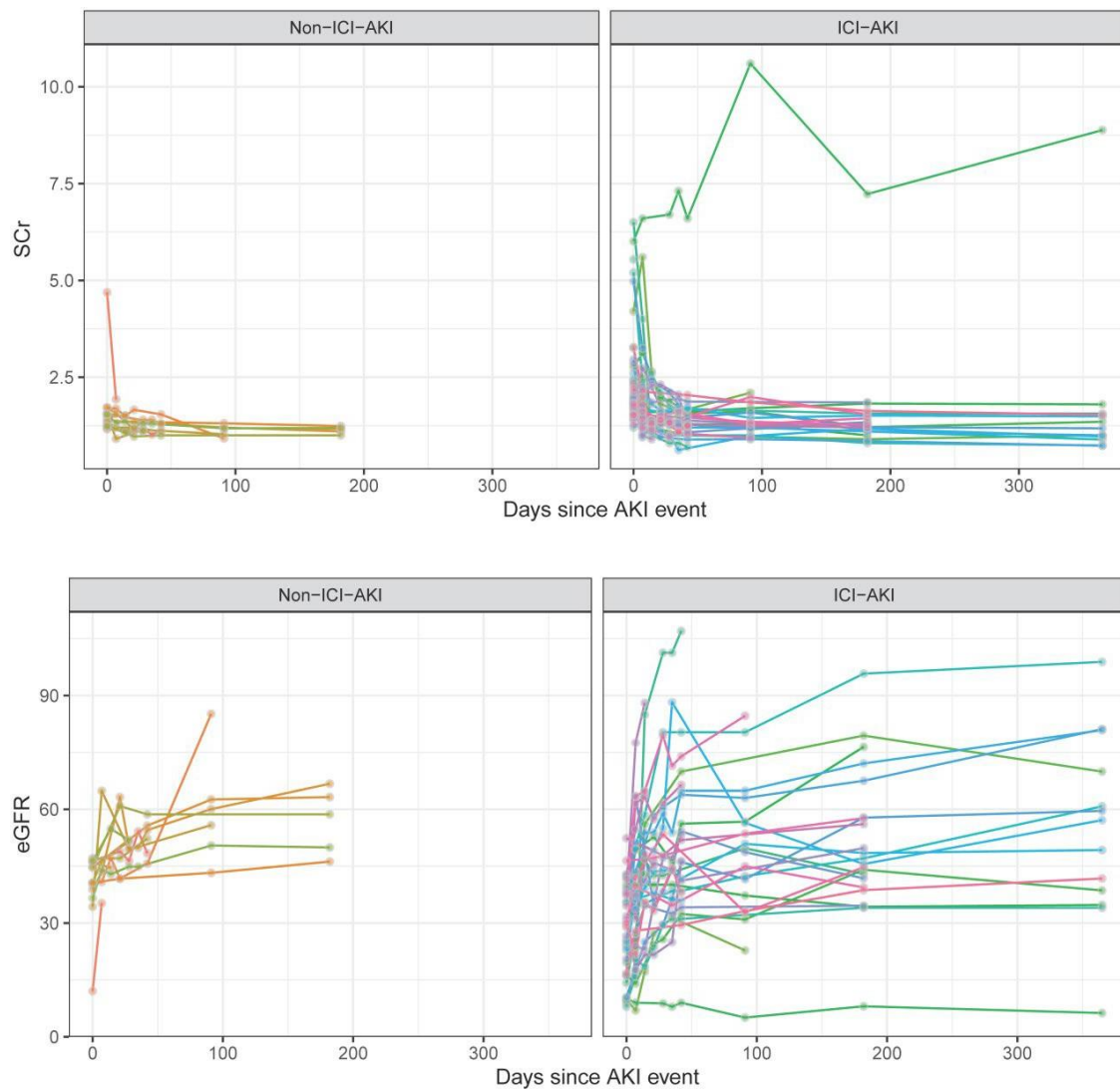
Biomarker	Time point	Non-ICI-AKI (N=13)		ICI-AKI (N=37)		Total (N=50)	
		N	Median [IQR]	N	Median [IQR]	N	Median [IQR]
<b>eGFR</b> (ml/min/1.73m <sup>2</sup> )	Baseline (Time of ICPi)	13	76.8 [68.1, 80.7]	37	77.9 [59.9, 89.5]	50	77.9 [62.6, 85.6]
	Time of AKI onset	13	40.6 [38.9, 46.0]	37	28.9 [16.7, 37.8]	50	34.4 [20.5, 40.6]
	7 Days after AKI onset	6	43.7 [40.8, 46.4]	31	36.2 [21.7, 49.2]	37	38.4 [23.9, 46.4]
	14 Days after AKI onset	4	45.8 [43.7, 51.0]	21	43.0 [34.6, 58.5]	25	44.5 [35.2, 56.1]
	21 Days after AKI onset	6	48.0 [41.7, 60.9]	18	43.0 [33.2, 49.1]	24	44.3 [36.2, 50.9]
	28 Days after AKI onset	6	49.6 [46.3, 51.6]	17	47.8 [38.3, 60.5]	23	49.4 [42.5, 58.9]
	35 Days after AKI onset	3	49.8 [44.9, 54.1]	20	42.0 [33.6, 46.6]	23	43.8 [34.7, 49.8]
	42 Days after AKI onset	6	53.4 [48.4, 55.7]	23	46.3 [36.0, 64.9]	29	51.9 [38.4, 58.7]
	3 months after AKI onset	6	57.9 [50.4, 62.6]	19	48.7 [33.2, 56.7]	25	50.4 [41.5, 60.1]
	6 months after AKI onset	5	58.7 [49.9, 63.2]	22	46.3 [39.4, 57.8]	27	48.5 [41.8, 63.2]
	1 year after AKI onset	0	-	13	57.1 [38.6, 69.9]	13	57.1 [38.6, 69.9]
<b>SCr</b> (mg/dl)	Baseline (Time of ICPi)	13	0.8 [0.8, 1.1]	37	0.9 [0.8, 1.1]	50	0.9 [0.8, 1.1]
	Time of AKI onset	13	1.5 [1.3, 1.6]	37	2.0 [1.7, 2.9]	50	1.8 [1.5, 2.6]
	7 Days after AKI onset	6	1.4 [1.2, 1.7]	31	1.7 [1.3, 2.4]	37	1.6 [1.3, 2.2]
	14 Days after AKI onset	4	1.4 [1.2, 1.5]	21	1.3 [1.2, 1.9]	25	1.4 [1.2, 1.8]
	21 Days after AKI onset	6	1.2 [1.1, 1.4]	18	1.5 [1.3, 1.7]	24	1.4 [1.2, 1.6]
	28 Days after AKI onset	6	1.2 [1.1, 1.3]	17	1.3 [1.0, 1.6]	23	1.3 [1.1, 1.4]
	35 Days after AKI onset	3	1.3 [1.0, 1.4]	20	1.6 [1.3, 1.7]	23	1.4 [1.2, 1.7]
	42 Days after AKI onset	6	1.2 [1.1, 1.3]	23	1.3 [1.1, 1.7]	29	1.3 [1.1, 1.5]
	3 months after AKI onset	6	1.2 [1.0, 1.2]	19	1.3 [1.2, 1.7]	25	1.2 [1.2, 1.6]
	6 months after AKI onset	5	1.2 [1.1, 1.2]	22	1.2 [1.1, 1.5]	27	1.2 [1.1, 1.5]
	1 year after AKI onset	0	-	13	1.2 [1.0, 1.5]	13	1.2 [1.0, 1.5]
<b>CRP</b> (mg/L)	Baseline (Time of ICPi)	4	41.5 [6.0, 105.5]	8	7.5 [3.0, 19.3]	12	9.5 [3.0, 30.8]
	Time of AKI onset	11	3.5 [3.0, 7.9]	13	54.0 [33.7, 90.0]	24	13.1 [3.3, 57.4]
	7 Days after AKI onset	2	5.3 [3.0, 7.6]	4	12.4 [3.2, 27.6]	6	5.5 [3.0, 21.4]
	14 Days after AKI onset	0	-	4	8.9 [5.8, 16.1]	4	8.9 [5.8, 16.1]
	21 Days after AKI onset	1	3.0 []	4	12.8 [5.4, 50.4]	5	5.5 [5.2, 20.1]
	28 Days after AKI onset	0	-	3	10.9 [3.0, 12.9]	3	10.9 [3.0, 12.9]
	35 Days after AKI onset	0	-	3	5.3 [3.0, 6.7]	3	5.3 [3.0, 6.7]
	42 Days after AKI onset	0	-	5	3.3 [3.0, 6.5]	5	3.3 [3.0, 6.5]
	3 months after AKI onset	1	3.0 []	2	4.3 [3.0, 5.6]	3	3.0 [3.0, 5.6]
	6 months after AKI onset	0	-	1	3.0 []	1	3.0 []
	1 year after AKI onset	0	-	0	-	0	-
<b>uRBP/Cr</b> (mcg/g Cr)	Baseline (Time of ICPi)	0	-	0	-	0	-
	Time of AKI onset	10	233 [127, 989]	7	1927 [1174, 46522]	17	989 [208, 1927]
	7 Days after AKI onset	3	989 [638, 13960]	3	14418 [4130, 79130]	6	9045 [989, 14418]
	14 Days after AKI onset	0	-	3	397 [200, 2300]	3	397 [200, 2300]
	21 Days after AKI onset	1	208 []	4	1537 [171, 8935]	5	340 [208, 2734]
	28 Days after AKI onset	0	-	1	6278 []	1	6278 []
	35 Days after AKI onset	0	-	3	134 [112, 11833]	3	134 [112, 11833]
	42 Days after AKI onset	0	-	5	417 [369, 16432]	5	417 [369, 16432]
	3 months after AKI onset	1	168 []	2	556 [473, 638]	3	473 [168, 638]
	6 months after AKI onset	0	-	2	1574 [129, 3018]	2	1574 [129, 3018]
	1 year after AKI onset	0	-	0	-	0	-

**Table S5.** Comparison of Characteristics among n=16 patients with ICI-AKI who were rechallenged, overall and by AKI status after rechallenge,

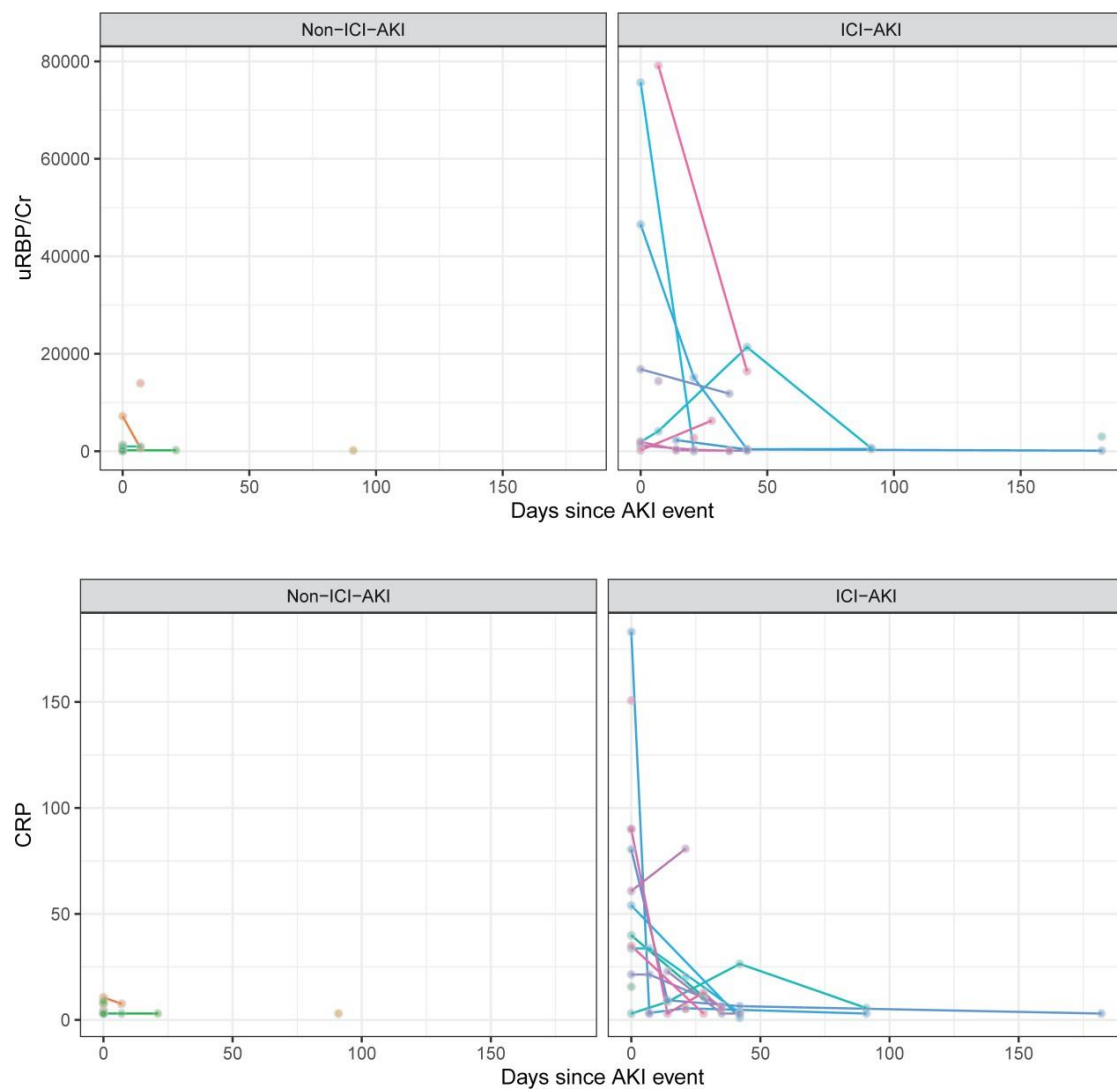
Characteristics of Rechallenge	No AKI after Rechallenge (N=13)	AKI after Rechallenge (N=3)	Total (N=16)	p value
Any AIN drugs at rechallenge, %y	3 (23.1%)	2 (66.7%)	5 (31.3%)	0.21
AIN Drug type, %y				
PPI	2 (15.4%)	2 (66.7%)	4 (25.0%)	0.14
NSAIDS	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Antibiotics	1 (7.7%)	0 (0.0%)	1 (6.3%)	>0.99
Prednisone dose at rechallenge, median [IQR]	10.0 [0.0, 20.0]	20.0 [10.0, 80.0]	10.0 [2.0, 20.0]	0.22



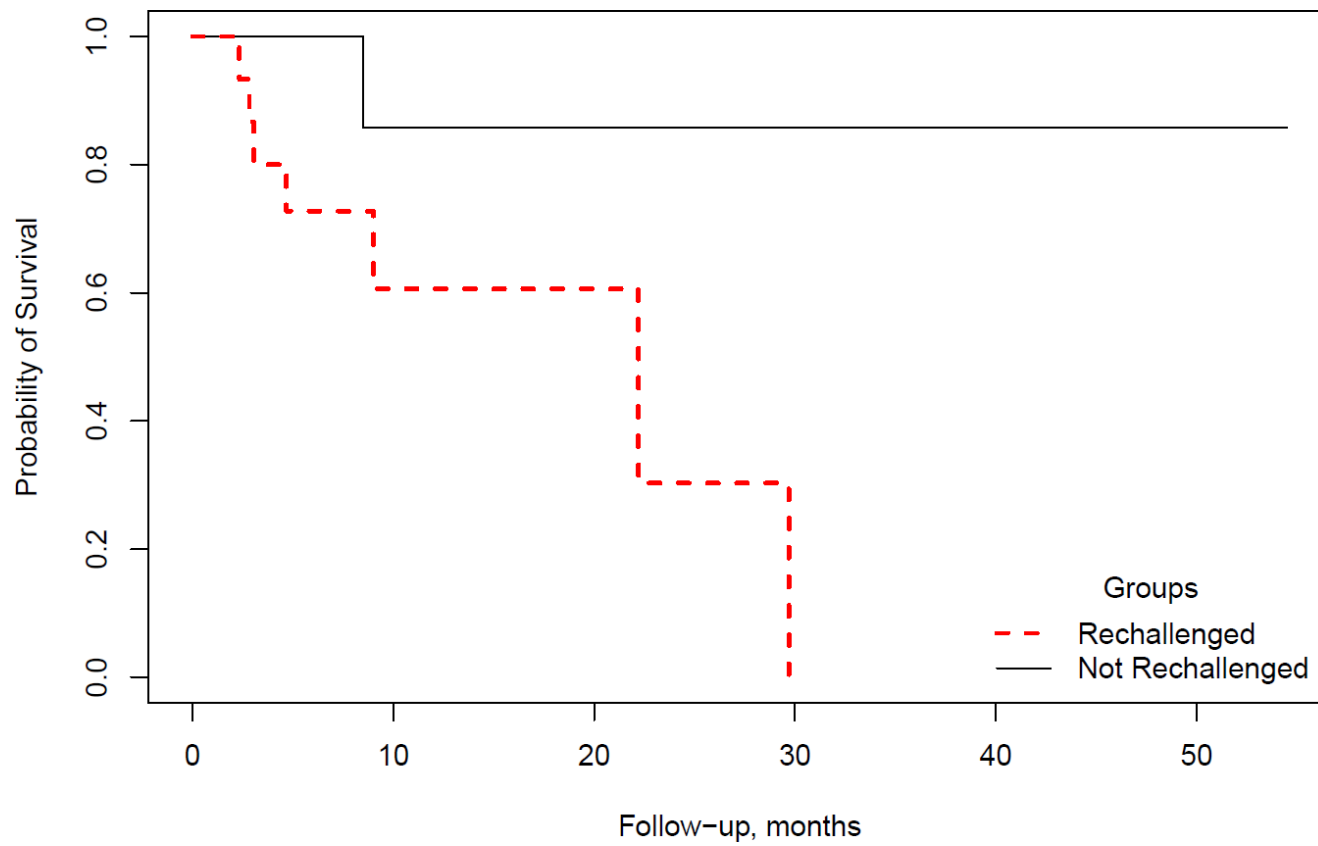
**Figure S1.** Boxplot overlaid with jitterplot of  $\log(\text{CRP} \cdot \text{uRBP}/\text{cr})$ , by cause of AKI.



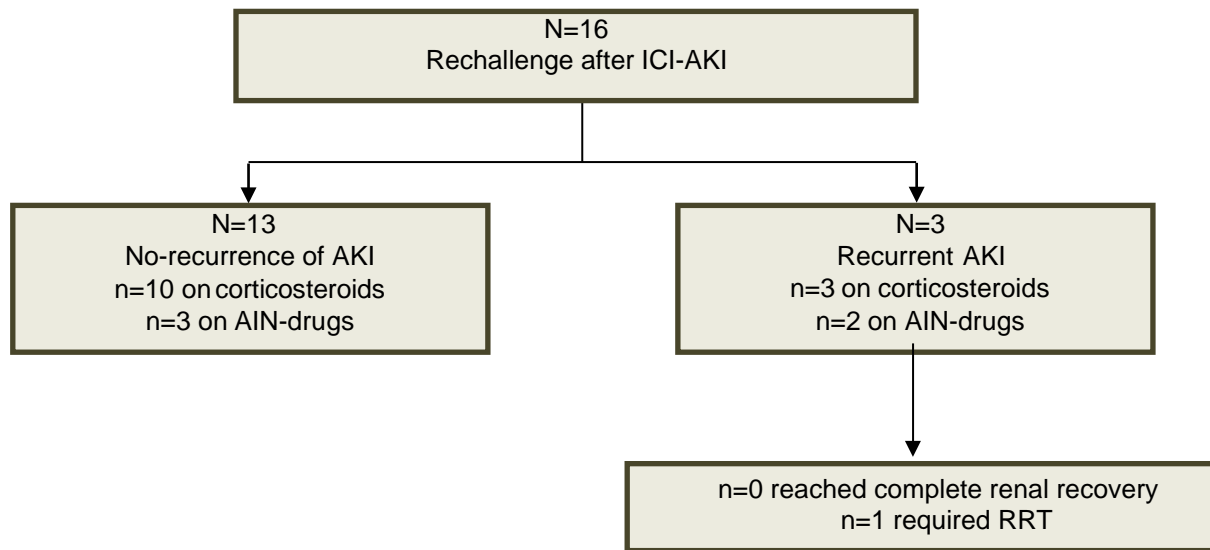
**Figure S2a.** Longitudinal patient trajectory data of kidney function over follow-up, by AKI cause



**Figure S2b.** Longitudinal patient trajectory data of biomarker labs over follow-up, by AKI cause



**Figure S3:** Kaplan Meier curve of survival time in months among those rechallenged vs not rechallenged



**Figure S4:** Flow chart of patients who were rechallenged and recurrence of ICI-AKI

# Modified STROBE Statement—checklist of items that should be included in reports of observational studies (Cohort/Cross-sectional and case-control studies)

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract ( <b>page 2</b> )
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found ( <b>page 2</b> )
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ( <b>page 3-4</b> )
Objectives	3	State specific objectives, including any prespecified hypotheses ( <b>page 4</b> )
Methods		
Study design	4	Present key elements of study design early in the paper ( <b>page 4</b> )
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ( <b>page 4-5</b> )
Participants	6 ( <b>page 4-5</b> )	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7 ( <b>page 4-5</b> )	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* ( <b>page 4</b> )	For each variable of interest, give sources of data and details of methods of assessment (measurement).
Bias	9 ( <b>page 15</b> )	Describe any efforts to address potential sources of bias
Study size	10 ( <b>page 7</b> )	Explain how the study size was arrived at (if applicable)
Quantitative variables	11 ( <b>page 5-6</b> )	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 ( <b>page 5-6</b> )	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed ( <b>page 6</b> )
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy
		(e) Describe any sensitivity analyses
Results		
Participants	13* ( <b>page 7</b> ) ( <b>Figure 1</b> )	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed (c) <b>Use of a flow diagram</b>

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ( <b>Table 1</b> )
		(b) Indicate number of participants with missing data for each variable of interest ( <b>Table 3 -4</b> )
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount) ( <b>Figure 3, figure 4, Figure S2 and S3</b> )
Outcome data	15* ( <b>Figure 4, Figure S2 and S3</b> )	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ( <b>page 7-12</b> )
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses <b>N/A</b>
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives ( <b>page 12</b> )
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ( <b>page 15</b> )
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ( <b>page 15-16</b> )
Generalisability	21	Discuss the generalisability (external validity) of the study results ( <b>page 16</b> )

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).